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Recommendations

Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis

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ABSTRACT

The management of spondyloarthritis is challenging and has changed with the development of new concepts and treatments.
Objective: To develop practice guidelines for the everyday management of patients with spondyloarthritis (including psoriatic arthritis), by updating previous national and international recommendations, based on a review of recently published data.
Methods: A task force and a multidisciplinary literature review group were established. The task force identified the issues that remained unresolved. Based on existing recommendations and recent publications, the task force developed practice guidelines, which were revised by the literature review group and graded according to AGREE.
Results: Practice guidelines for the management of spondyloarthritis are reported. After a review of the general diagnostic principles, 30 practice guidelines are given: 5 on general principles, 4 on the management strategy, 5 on non-pharmacological treatments, 7 on conventional pharmacological treatments, 6 on biotherapies, and 3 on surgical treatments and follow-up.
Conclusion: The updated practice guidelines reported here constitute a global framework that can guide physicians in the everyday management of spondyloarthritis.

1. Introduction: the setting

The term "spondyloarthritis" designates an array of rheumatic diseases responsible for a variety of clinical pictures. The field of spondyloarthritis has undergone major changes in recent years, regarding not only the nosology and classification, but also the investigations (most notably imaging studies) and, above all, treatments, with the introduction of TNFα antagonists. Consequently, the French Society for Rheumatology (*Société française de rhumatologie*, [SFR]) has developed practice guidelines for spondyloarthritis based on the previous recommendations and recently published data.

2. Methodology

The overall objective is to develop practice guidelines for spondyloarthritis based on an update and French adaptation of existing recommendations issued by the ASAS/EULAR and ASAS (Assessment in Spondyloarthritis International Society) [1,2]. To

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this end, we followed both the general principles put forward in AGREE II [3] and EULAR rules for developing recommendations [4].

Our starting point was the set of ASAS/EULAR recommendations for managing ankylosing spondylitis [1] and the updated recommendations on TNFα antagonist therapy in spondyloarthritis [2], with the corresponding literature reviews [5,6], recommendations on psoriatic arthritis [7,8], and French recommendations on TNFα antagonist therapy, specifically in spondyloarthritis and psoriatic arthritis [9] and generally in rheumatic diseases [10]. We also took into account recent recommendations on targeted treatments [11], with their underlying evidentiary base [12].

We constituted a task force whose coordinator was a project director appointed by the SFR (DW). This group was composed of rheumatologists considered by the SFR to be experts in spondyloarthritis, a rheumatologist specialized in methodology and epidemiology, and a patient with spondyloarthritis who was a member of a patient self-help organization. A systematic literature review was conducted by two university-hospital rheumatologists who were trained in literature reviews (CL, JP). Articles published between January 1, 2010, and June 17, 2013, were retrieved using appropriate key terms to search PubMed-Medline, Cochrane, and Embase. In addition, a manual search of article reference lists and EULAR and ACR meeting abstracts was performed. The level of evidence of each publication was assessed. In preliminary work, the task force identified unresolved issues and points requiring updates. A physical meeting was held for presentation of the literature review data, discussion among experts, and development of the practice guidelines. Subsequently, the practice guidelines were reviewed by the same experts for validation and rating of the level of agreement, from which the grade of each practice guideline was determined. Finally, the practice guidelines were submitted to a group of reviewers designated by the task force and described below. The final version was modified based on the comments by both groups.

3. Target of the practice guidelines

These practice guidelines are intended for physicians and other healthcare professionals involved in managing patients with spondyloarthritis. However, their global scope makes them chiefly relevant to rheumatologists. A document intended for patients will be developed.

4. Conceptual definition of spondyloarthritides: the diseases involved

These practice guidelines are relevant to all adults who meet current classification criteria. These criteria have evolved over time, in particular, with the introduction of new imaging studies, most notably magnetic resonance imaging (MRI) of the sacroiliac joints used for diagnostic purposes. The ASAS has issued classification criteria for axial [13] and peripheral [14] forms of spondyloarthritis. Thus, these practice guidelines apply overall to patients meeting ASAS criteria, as well as to patients meeting other criteria sets, such as those developed by Amor et al. and the ESSG [15], whose validity remains undeniable.

5. Terminology

The term "spondyloarthritis" encompasses several disease phenotypes, including the classical nosological entities (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthropathies, and undifferentiated spondylarthropathies). Thus, the term used to designate all these diseases is "spondyloarthritis" [16], which has replaced the term "spondylarthropathy" (Table 1).

Table 1
Suggested terminology for describing the clinical phenotype of patients with spondyloarthritis [16].

Axial spondyloarthritis
Radiographic[a] (including ankylosing spondylitis)
Non-radiographic[a]
Spondyloarthritis with peripheral joint involvement
Erosive[a]
Non-erosive[a]
Spondyloarthritis with peripheral enthesitis[a]

[a] Add any concomitant extraarticular manifestations to better characterize the phenotype (with psoriasis, Crohn's disease, ulcerative colitis, and anterior uveitis).

Non-radiographic axial spondyloarthritis is a new concept individualized by current criteria [17]. This classification incorporates, among other diseases, psoriatic arthritis with its various phenotypic presentations, which are forms of spondyloarthritis. Thus, these practice guidelines apply to psoriatic arthritis manifesting as axial disease, peripheral joint disease, or peripheral enthesitis.

6. Diagnosis

The early diagnosis of spondyloarthritis is challenging and rests on a combination of findings from the medical history, physical examination, laboratory tests, and imaging studies, on which the expert can base an opinion. The task force emphasizes the importance of strict adherence to the definitions of the items in the criteria sets, to ensure their validity. This requirement applies also to the imaging criteria, most notably, the MRI criteria. The risk of overdiagnosis should be acknowledged and taken into account [18].

At present, the imaging study sign used to establish the diagnosis is an MRI finding of subchondral bone marrow edema in the sacroiliac joints, on at least two consecutive sections if a single topographic zone is abnormal; or of bone marrow edema in at least two different periarticular sites. To be valid, these abnormalities must be unequivocal and sufficiently extensive to rule out a non-specific lesion or artefact, particularly of a vascular nature [19]. It is important to be aware, however, that these findings are inconsistent: some patients with a definite diagnosis of spondyloarthritis and clinical or laboratory evidence of disease activity have normal MRI findings. MRI of the spine can benefit the initial management of the patient, not only to rule out differential diagnoses (e.g., benign or malignant spinal tumors, infections of the disks and vertebras, or inflammatory disk disease), but also to detect other lesion types that suggest spondyloarthritis and may therefore support the diagnosis. Thus, the presence of a large number of "inflammatory" signals or of fatty involution at the vertebral corners lends some support to the possibility of spondyloarthritis when combined with back pain, particularly in younger patients with involvement of a large number of vertebras. Nevertheless, these MRI abnormalities can be found in non-specific low back pain, vertebral malignancies, and even healthy individuals and, when isolated, are consequently not sufficient to establish a diagnosis of spondyloarthritis. Recent studies have shown that repeating the MRI scans fails to benefit the diagnosis. Finally, the task force points out that criteria intended solely for classification purposes should be used for diagnostic purposes only with the utmost caution.

The work presented here does not apply to pediatric spondyloarthritis, since the ASAS criteria are not relevant to children, in whom the clinical presentation is often different from that seen in adults. In addition, the therapeutic trials referred to in these practice guidelines were conducted only in adults.

7. Practice guidelines

The strength of the practice guidelines (based on the level of evidence) and the level of agreement among experts (rated from 0 [strongly disagrees] to 10 [strongly agrees]) are given for each

practice guideline. Strength was graded according to standard practice:

- A: guideline based on level 1 evidence (meta-analysis of randomized controlled trials or at least one randomized controlled trial);
- B: guideline based on level 2 evidence (at least one nonrandomized controlled trial or quasi-experimental study) or extrapolated from level 1 evidence;
- C: guideline based on level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence;
- D: guideline based on level 4 evidence (expert opinion) or extrapolated from level 1, 2, or 3 evidence.

7.1. General principles

1) Spondyloarthritis (SpA) is a potentially severe and disabling chronic illness characterized by a variety of manifestations. The management of patients with spondyloarthritis should be coordinated by a rheumatologist, usually in connection with a multidisciplinary team, in collaboration with the primary care physician (C) (10).

Spondyloarthritis is a potentially severe disease associated with a decrease in life expectancy [20,21]. Although the clinical presentation shows extraordinary variability across patients, all the most common manifestations – inflammatory back pain, peripheral arthritis, and extraarticular signs – are incapacitating symptoms responsible for pain, temporary or permanent functional impairments [22], and adverse effects on everyday life (e.g., asthenia and reactive depression) [23]. Consequently, spondyloarthritis requires a multidisciplinary approach involving various physicians and other healthcare professionals whose work is coordinated by the rheumatologist and conducted in collaboration with the primary care physician as part of the usual chain of care.

2) The objectives in patients with spondyloarthritis are to improve the quality of life; control the symptoms and inflammation; prevent structural damage, particularly in forms with peripheral arthritis; and preserve or restore functional capabilities, self-sufficiency, and social participation (D) (10).

The overall management should ensure the control of all the dimensions of the disease.

3) The treatment rests on medical decisions shared with the patient (D) (9,8).

4) The optimal management consists of a combination of pharmacological and non-pharmacological means (D) (10).

5) The diagnosis should be established and the management initiated as early as possible (C) (9,7).

Although early disease management has not been proven to ameliorate the long-term outcomes of patients with spondyloarthritis, several lines of evidence suggest benefits from early diagnostic confirmation and prompt treatment initiation. The achievement of optimal symptom relief and initiation of the non-pharmacological components of the management strategy cannot be started until a definite diagnosis is made. The mean time from symptom onset to the diagnosis of spondyloarthritis is still 7 years [23]. Furthermore, a longer time to diagnosis is associated with excess mortality in ankylosing spondylitis [21].

7.2. Management strategy

6) The goal of management should be to achieve a clinical remission or a low level of disease activity, as assessed based on the various components of the illness (axial, peripheral, and extraarticular manifestations) and on the co-morbidities. Close monitoring of the patient by the rheumatologist until this goal is achieved may be required. Once the goal is achieved, regular individualized follow-up should be provided to ensure that it is maintained (D) (9,7).

The various therapeutic tools available to the physician and patient to control disease activity provide major benefits in most situations and, consequently, ambitious goals should be set. As with other chronic illnesses, a reasonable treatment objective is the achievement of a remission or at least of a low level of disease activity, in compliance with the recent European "treat-to-target" recommendations [11]. At present, there is no definition or set of operational and universally accepted criteria for disease remission in the various phenotypic forms of spondyloarthritis. To fill this gap, the definition of a partial remission developed by the ASAS for therapeutic trials of NSAIDs [15] or the ASDAS activity cut-offs (with a score lower than 1.3 defining inactive disease) can be used [24].

There is no evidence to date to support the use of imaging studies (most notably MRI) for patient follow-up. The relevance of MRI to patient follow-up is unknown. The initial treatment phase, during the period that surrounds and immediately follows the diagnostic workup, requires closely spaced follow-up evaluations to assess the full range of manifestations and their impact on the patient, the course under treatment and possible need for treatment adjustments, and the tolerance of the treatment.

7) Smoking is associated with increased disease activity and severity, and smoking cessation can therefore be expected to benefit the course of the disease, in addition to improving general health (C) (9,3).

The adverse effects of smoking in terms of cardiovascular disease, lung disease, and malignancies are well established. In addition, smoking has been demonstrated to adversely affect the course of spondyloarthritis (disease activity, Health Assessment Questionnaire [HAQ] scores, and radiographic progression were worse in smokers than in non-smokers with SpA) [25]. These effects constitute an additional argument in support of smoking cessation in patients with spondyloarthritis.

8) The rheumatologist should evaluate the disease by investigating the various domains involved (disease activity, dependency on anti-inflammatory drugs, and disease severity [inflammatory hip disease, functional impairments, incapacitating extraarticular manifestations, and structural damage]) and assessing the course over time (D) (9,5).

No validated definitions or criteria for spondyloarthritis are available to date. Marked and persistent inflammatory activity and failure to respond to treatments may provide orientation.

In the opinion of the task force, markers for disease severity include a high level of disease activity that persists despite treatment, a need for continuous maximal dose NSAID therapy to control the symptoms, severe functional impairments (as shown by the BASFI, HAQ score, and difficulties at work and with social activities), the existence and course of structural damage (particularly at peripheral sites), inflammatory hip disease, and severe extraarticular manifestations (severe recurrent acute anterior uveitis and involvement of the heart and lungs). These markers are similar to the items listed in the guide of the French National Authority for Health (*Haute Autorité de santé* [HAS]) for obtaining full reimbursement of healthcare costs (Table 2).

The predictors of severe outcomes reported by Amor in 1994 can be used also:

- inflammatory hip disease,
- erythrocyte sedimentation rate > 30 mm,
- poor response to NSAIDs,
- range-of-motion limitation at the lumbar spine,
- "sausage" finger or toe (dactylitis),
- oligoarthritis,
- and onset ≤ 16 years of age,

Table 2
Severity of spondyloarthritis according to the guide issued by the French National Authority for Health (*Haute Autorité de santé* [HAS]; Guide ALD nº 7, *Spondylarthrite grave*, HAS/*Service des bonnes pratiques professionnelles*/December 2008) (www.has-sante.fr).

Spondyloarthritis is classified as severe if any of the following criteria is met
Presence of a clearly severe manifestation, such as
Destructive arthritis, particularly involving the hip
Concomitant severe extraarticular manifestations, such as
Severe chronic inflammatory bowel disease (IBD)
Recurrent uveitis
Or severe spondyloarthritis-related heart disease (aortic or mitral valve disease, myocardiopathy, pericarditis, atrioventricular conduction disorder)
Any of the following findings present by physician examination on at least two occasions (3 months apart), despite NSAID therapy in the maximal recommended or tolerated dosage
Concomitant inflammation of more than three joints
Active spondyloarthritis with a BASDAI > 4 on a 0–10 scale
Or major spondyloarthritis-related functional impairment (in particular, BASFI > 4 on a 0–10 scale)
Continuous NSAID therapy in the maximal recommended or tolerated dosage needed to control the symptoms

• absence of all these items predicts favorable disease outcomes.

9) Follow-up intervals and modalities should be individualized depending on the presentation, course and treatment of the disease. Follow-up should include physician visits, the use of self-evaluation tools, and investigations. At least one tool for evaluating disease activity must be used. Access to the rheumatologist or to other specialists should be facilitated when patients experience intercurrent events (flare of joint disease, extraarticular manifestations, infectious diseases, life project. . .) (D) (9,5).

The presentation and activity of the disease vary over time in a given patient, and predicting the course of the disease is difficult. This fact, together with the broad range of drugs available for treating spondyloarthritis, precludes the definition of optimal follow-up intervals or modalities applicable to all patients. Nevertheless, the chronic nature of spondyloarthritis warrants a routine minimal follow-up, for instance, once a year, to evaluate the course of the disease, detect any complications or new manifestations, and evaluate healthcare service utilization; follow-up should be adjusted to the symptoms and disease progression. Involvement of axial and/or peripheral joints requires the use of an appropriate tool for evaluating the initial status and changes over time; this tool should be selected among those available to date [15]. In patients with axial involvement, the BASDAI (associated with C-reactive protein level) and/or ASDAS should be used to measure disease activity and the BASFI to assess the functional impact. In patients with predominant or concomitant peripheral involvement, preference should be given to the tender and swollen joint counts and to activity indicators, such as the DAS; in psoriatic arthritis, the PASDAS and PsARC can be used. In the event of extraarticular manifestations, specific tools may be helpful. According to the specific nature of the manifestations experienced by the patient, access to the specialist who is in the best position to provide appropriate care should be facilitated, depending not only on the symptoms (e.g., pain due to arthritis or diarrhea due to a bowel flare), but also on the potential severity of the manifestations (e.g., risk of adhesions or permanent vision loss due to the delayed treatment of acute anterior uveitis).

7.3. Non-pharmacological management

10) Information, health education, and therapeutic education are integral components of the management of patients with spondyloarthritis (C) (9,8).

In an open-label prospective study, a 4-day therapeutic education program (information classes, individual and group physiotherapy sessions, and discussion) significantly improved both knowledge about the disease and motion range of the hips and spine [26].

In severe forms, in compliance with French regulations, the primary care physician can request full coverage of all spondyloarthritis-related healthcare costs by the statutory health insurance system. Other measures can be taken according to French legislation relevant to disability compensation and occupational medicine.

11) Patient organizations or organizations that focus on health and/or assistance may be of help (D) (9,4).

12) Although home exercises, most notably home programs, are effective, physical therapy with supervised exercises, particularly in a pool, as individual or group sessions, should be given preference given its greater effectiveness in axial forms of spondyloarthritis (B) (9,1).

This recommendation is particularly relevant to patients with axial involvement as assessed clinically (motion range limitation) or radiographically.

Recent publications on this topic [27–33] confirm the beneficial effects of rehabilitation therapy and self-rehabilitation programs on indices measuring disease activity and function (BASDAI and BASFI). For instance, a randomized controlled trial in 62 patients with ankylosing spondylitis in Italy compared rehabilitation therapy (12 sessions) plus two therapeutic education sessions to therapeutic education alone and to a control group. Rehabilitation therapy was associated with significantly greater improvements in the BASDAI, motion ranges, and BASFI, which persisted 6 months later [33].

13) The extraarticular manifestations (psoriasis, uveitis, chronic inflammatory bowel disease) should be managed in collaboration with the appropriate specialists (D) (9,5).

The treatment decisions, follow-up, and dosage adjustments of certain specific drugs, as well as the evaluation of certain disease manifestations (gastrointestinal and ophthalmological in particular) require the involvement of appropriate specialists to optimize disease control and obtain the best possible long-term outcomes.

14) As part of the follow-up of this chronic disease, an important task for the rheumatologist is to ensure that appropriate screening and management of co-morbidities are provided, including for osteoporosis, in compliance with current recommendations (D) (9,2).

Attention should be directed to the development of co-morbidities in patients with spondyloarthritis, as is the case with all chronic inflammatory diseases. The spondyloarthritis may worsen the co-morbidities (particularly cardiovascular co-morbidities), which also limit the use of various drug classes [34].

Cardiovascular co-morbidities deserve special attention, as well as osteoporosis, whose prevalence is increased in patients with spondyloarthritis [35–38]. The overall management of co-morbidities should be conducted in collaboration with the primary care physician.

7.4. Treatment with conventional medications

15) In the absence of contraindications, NSAIDs constitute the first-line pharmacological treatment of symptomatic spondyloarthritis (A) (10).

In most patients, NSAID therapy effectively controls the joint symptoms and signs of spondyloarthritis [39,40]. NSAIDs have non-significant effects on laboratory markers for inflammation [39]; in contrast, various results suggest a beneficial effect on axial structural damage [41]. When NSAIDs are contraindicated, analgesics and physical therapy should be given preference to the first-line treatment. The response to a given NSAID varies across

individuals, and several NSAIDs should therefore be tried before concluding that this drug class is not effective.

16) The NSAID regimen should be tailored to each individual patient, and the lowest dosage and duration ensuring symptom control should be used. When selecting the NSAID, the risks of adverse cardiovascular, gastrointestinal, and renal effects should be among the factors taken into consideration (C) (9,7).

Before initiating NSAID therapy, the cardiovascular, gastrointestinal, and renal risk factors should be assessed. The risk profile varies across NSAIDs and, consequently, the presence of specific patient characteristics should be taken into account when selecting the NSAID. For instance, a COX2 inhibitor should be given preference in patients with gastrointestinal risk factors and naproxen in those with cardiovascular risk factors. All patients should be monitored carefully and regularly for adverse effects. Given the risks associated with continuous full-dose NSAID therapy, the lowest dose that ensures disease control should be sought [42,43].

17) Analgesics can be used in patients with residual pain despite NSAID therapy and in patients with failure of, contraindications to, or intolerance to NSAIDs (D) (9,8).

No data on analgesic treatments in spondyloarthritis have been published recently [44].

18) Local glucocorticoid injections at symptomatic sites (most notably sites of arthritis or enthesitis) can be considered (D) (9,8).

The evidentiary basis for this guideline is described in the previous recommendations. The only recent data come from a non-randomized study comparing locally injected betamethasone ($n = 7$) to locally injected etanercept in patients with refractory enthesitis. Significant improvements occurred in both groups with no significant between group difference after 12 weeks [45].

19) In general, systemic glucocorticoid therapy is not warranted for treating the axial manifestations of spondyloarthritis (D) (9,7).

Given the numerous and potentially severe adverse effects of systemic glucocorticoid therapy, together with the paucity of published data, this treatment is not warranted for the axial manifestations of spondyloarthritis. The only therapeutic trial of systemic glucocorticoid therapy included a limited number of patients ($n = 39$) who had an inadequate response to NSAID therapy; in addition, the trial evaluated high dosages (50 mg/d versus 20 mg/d versus placebo) [46] given for only 2 weeks. Consequently, the improvements recorded with the higher dose cannot be construed as supporting the widespread use of this treatment. However, systemic glucocorticoid therapy may deserve consideration when the peripheral joint manifestations are not satisfactorily controlled, in the absence of effective or feasible treatment options (e.g., in patients with contraindications to TNFα antagonist therapy) or in unusual situations (e.g., flare associated with inflammatory bowel disease). In these cases, the lowest possible dosage of systemic glucocorticoid must be used.

20) To date, there is no indication for conventional disease-modifying antirheumatic drugs ([DMARDs], methotrexate, leflunomide, and sulfasalazine) to treat isolated axial manifestations or enthesitis (C) (9,3).

Since the publication of the previous recommendations, no studies have produced evidence that conventional DMARDs are effective on the axial manifestations. For methotrexate, a *Cochrane review* published in 2013 [47] found no new studies since 2007. Two randomized trials from Germany compared etanercept and sulfasalazine in patients with axial spondyloarthritis [48–50]; etanercept was superior over sulfasalazine for the various outcome measures studied (ASAS20, ASAS 40, and partial remission). The absence of a placebo group precluded an evaluation of the effects of sulfasalazine.

21) The use of conventional DMARDs (methotrexate, leflunomide, and sulfasalazine) can be considered in patients with peripheral arthritis that fails to respond to symptomatic therapy (D) (9,8).

There is little or no scientific evidence on this point [51,52]. Nevertheless, clinical experience supports a beneficial effect of conventional DMARDs (methotrexate, leflunomide, and sulfasalazine), whose use can be considered in patients with peripheral arthritis that is inadequately controlled by NSAIDs and/or local glucocorticoid injections. The DMARD should be selected on a case-by-case basis, according to the patient's profile. For instance, preference should be given to methotrexate in patients with cutaneous psoriasis. In France, leflunomide and methotrexate are licensed for use in psoriatic arthritis. No studies have assessed the potential structural effects of conventional DMARDs on peripheral joints. Some conventional DMARDs (sulfasalazine, methotrexate) may also improve the extraarticular manifestations (uveitis, bowel disease). Experts agree that conventional DMARDs are not indicated in patients with isolated entheseal involvement, a situation about which no scientific evidence is available [5,7,8].

7.5. Biologic agents

22) TNFα antagonist therapy should be offered to patients with persistent disease activity despite conventional treatment, according to the recommendations shown in Fig. 1 (D) (9,8).

Fig. 1 recapitulates the recommendations for using TNFα antagonists according to the clinical presentation (phenotype), when the conventional treatment fails or induces an inadequate response with persistent disease activity and objective evidence of inflammation. When objective evidence of inflammation is lacking, the opinion of experts is taken into account. The presence and progression of extraarticular manifestations should also be taken into consideration. The generally applicable indications can be modulated according to a number of factors, such as the amount of NSAIDs required on a daily basis, in the light of the risk/benefit ratio for each treatment option.

An inadequate response to NSAID therapy can be defined either as persistence of symptoms despite maximal dosage NSAID therapy or as persistent disease activity with a BASDAI $\geq 4/10$ or an ASDAS ≥ 2.1 during NSAID therapy.

The initiation and follow-up of TNFα antagonist therapy should be conducted according to the current recommendations and practice guidelines: overall management of TNFα antagonists as described in the CRI fact sheets CRI [10] and recommendations issued by the SFR/CRI/HAS [53].

A number of factors that predict a good response to TNFα antagonist therapy have been identified in patients with spondyloarthritis [54]: systemic evidence of inflammation at baseline (CRP), high values of disease activity and functional impairment scores, young age, presence of HLA-B27, peripheral arthritis, and male gender are independently associated with a treatment response and with treatment continuation. In contrast, obesity is associated with a poorer response to TNFα antagonists in both ankylosing spondylitis [55] and psoriatic arthritis [56]. The presence of one or more of these factors may influence the decision to start TNFα antagonist therapy. Nevertheless, the absence of factors associated with a good response does not warrant a decision against TNFα antagonist therapy in patients who meet criteria for this treatment.

All the TNFα antagonists available to date for use in spondyloarthritis have been proven effective in various forms of the disease [17,57–59]. TNFα antagonist therapy improved the symptoms and signs of spondyloarthritis, quality of life, productivity, and bone mineral density. The safety profile of TNFα antagonists in spondyloarthritis is similar to the overall safety profile of these

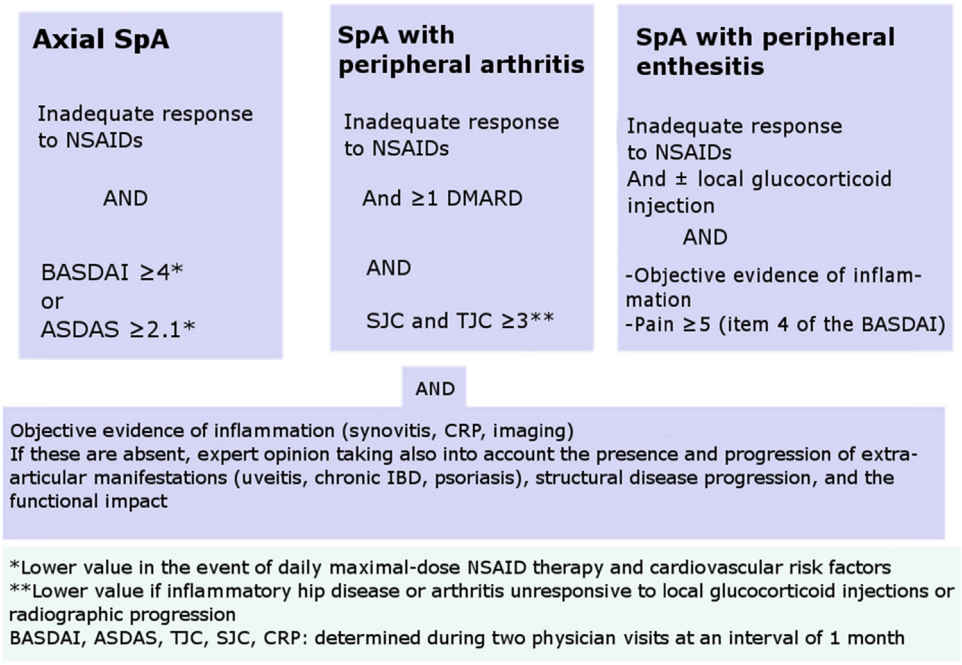

Fig. 1. Indications for TNFα antagonist therapy.

drugs [10,53]. It is worth noting that some patients may experience paradoxical effects [57], defined as the occurrence during TNFα antagonist therapy of manifestations that are among the indications for TNFα antagonists (e.g., uveitis, psoriasis, or de novo Crohn's disease at a time when the rheumatic manifestations of spondyloarthritis are well controlled by TNFα antagonist therapy).

Routine prescription of a conventional DMARD in combination with the TNFα antagonist is unnecessary [60]. Pivotal studies have established that single-drug therapy with a TNFα antagonist is effective, and there is no evidence to date that further benefits can be obtained by adding a conventional DMARD to a TNFα antagonist in patients with spondyloarthritis, including psoriatic arthritis [61]. Whether combined treatment with a conventional DMARD may help to diminish the immunogenicity of TNFα antagonists (most notably the monoclonal antibodies) is a controversial point that is currently under investigation.

Patients may develop an immune response against biological agents (anti-drug antibodies, ADAb). Such a response is more common with monoclonal antibodies against TNFα. It is often accompanied with an increased frequency of adverse reactions (particularly infusion reactions) and with diminished effectiveness [62].

In every case, the individual risk/benefit ratio should be taken into account when making the treatment decision.

23) The response to TNFα antagonist therapy should be evaluated after at least 3 months, using objective measures of disease activity (D) (9,1).

Examples of such measures are the decrease in NSAID consumption (ASAS-NSAID score) [63] or the percentage of days without NSAID use; a BASDAI decrease by 50% or by 2 points; an ASDAS decrease by more than 1.1 point [24] or an ASAS 20 or ASAS 40 response or an ASAS partial remission [15]; and the DAS-based EULAR response in patients with peripheral arthritis. Tests to monitor the initial systemic inflammation can also be included in the evaluation. Effectiveness is assessed based on the symptoms and signs. In everyday practice, follow-up imaging studies (e.g., MRI or radiographs) are unnecessary for evaluating the treatment response. At present, the possibility that TNFα antagonists may induce a radiographic structural response rests on a limited number of studies [64].

Effects on the extraarticular manifestations should be recorded.

In addition to the clinical response, safety data should be taken into account when deciding whether to continue the treatment.

24) In the event of primary or secondary lack of effectiveness of a TNFα antagonist, there is no proof to date that increasing the dosage is beneficial. After reappraising the diagnosis of spondyloarthritis and ruling out a differential diagnosis or complication of the disease, a switch to another TNFα antagonist deserves consideration (D) (9,7).

Switching to a second TNFα antagonist may be beneficial, in particular in the event of escape phenomenon, primary ineffectiveness, or intolerance to a first TNFα antagonist (C) (9,7).

Several studies found no advantages to high-dose etanercept therapy, including the PRESTA trial in psoriatic arthritis [65] and LOADET in ankylosing spondylitis [66], in which doubling the dose conferred no benefits compared to the standard dose at treatment initiation.

In this situation, monitoring the serum levels of the biological agent and, if appropriate, performing tests for antibodies against the biological agent, may provide a more accurate analysis and help to adjust the dosage [67].

In non-responders, an evaluation should be performed to determine that the symptoms are related to the inflammatory activity of the spondyloarthritis.

The option of switching to another TNFα antagonist rests on observational data from cohorts and registries for axial spondyloarthritis [68,69] and psoriatic arthritis [70]. In these studies, the continuation rate of a second TNFα antagonist was close to, but lower than, that of the first-line TNFα antagonist; in contrast, lower continuation rates were found for the third TNFα antagonist.

25) In the event of a disease remission or low level of activity sustained for at least 3 to 6 months under TNFα antagonist therapy, a gradual increase in the dosing interval or decrease in the drug dosage can be considered (C) (9,6).

Several studies show that the dosing interval can be increased or the dosage reduced in the event of a stable prolonged remission

[71–73]. This adjustment decreases the cost of treatment. It should be conducted gradually and under clinical supervision, given the risk of a disease flare during the decrease in drug exposure; if a flare occurs, the patient should be returned to the previous dosing interval or dosage.

26) There is no evidence to support differences across TNFα antagonists regarding effectiveness on the axial or peripheral manifestations/enthesitis. In patients with chronic inflammatory bowel disease (IBD), there is a difference in effectiveness on the gastrointestinal manifestations, which should be taken into account. (D)(9.7).

No head-to-head comparisons of various TNFα antagonists have been conducted in patients with spondyloarthritis. Consequently, no data are available for establishing a hierarchy of TNFα antagonists. Among TNFα antagonists, only monoclonal antibodies to TNFα have been proven effective on the manifestations of inflammatory bowel disease.

27) There is no evidence to date to support the use of biological agents other than TNFα antagonists in patients with axial spondyloarthritis (D) (9,6).

In patients who fail treatment with conventional DMARDs and TNFα antagonists, no treatment options exist [74]. Abatacept has not been proven effective [75]; rituximab is not effective in patients having failed TNFα antagonist therapy and remains to be evaluated in biotherapy-naive patients with peripheral joint manifestations [76–78]. Retrospective data on IL-6-antagonists are inconclusive [79] and controlled studies show no effect [80]. Options currently under investigation for spondyloarthritis and psoriatic arthritis include the anti-IL-17 secukinumab [81,82], the anti-IL-23 ustekinumab [83], and apremilast [84,85]. Ustekinumab (anti-p40 IL-12/23) is licensed for use in patients with psoriatic arthritis and an inadequate response to the conventional treatment.

7.6. Surgical treatments

28) Total arthroplasty can be offered to patients of any age who have structural joint damage responsible for refractory pain and severe functional impairments (D) (10).

This practice guideline applies chiefly to the hip [86]. The risk of subsequent development of a periprosthetic ossification should be evaluated.

29) In exceedingly rare cases, spinal osteotomy deserves consideration to correct severe incapacitating spinal deformities (D) (9,2).

The indications for this procedure have become exceedingly rare. The goal is to restore the horizontal line of vision. Useful functional improvements can be obtained but the procedure is challenging to perform and associated with specific complications (intubation difficulties, vascular and neurological complications).

30) In patients with a spinal fracture that occurred recently or has failed to heal, advice from a spinal surgeon should be sought. In the event of a significant and/or abrupt change in the symptoms, causes other than inflammation, such as a spinal fracture, should be considered and sought using appropriate investigations, including imaging studies (D) (9,7);

Fractures in a fused spinal segment carry a risk of instability, which can induce neurological complications. The possible presence of osteoporosis in patients with spondyloarthritis should be borne in mind. Commonplace osteoporotic vertebral fractures are low-risk events that should be distinguished from more specific fractures in a fused spinal segment with a fracture line through a disk or vertebral body.

Close attention should be given to patient follow-up, and during follow-up the symptoms should be analyzed carefully.

8. Research agenda

Several unresolved issues regarding the management of patients with spondyloarthritis were identified by the task force:

- definition and criteria of remission in spondyloarthritis (depending on the phenotypic form);
- definition and criteria of disease flare (depending on the phenotypic form);
- definition and criteria of severity of spondyloarthritis;
- role for the structural damage, particularly to the axial skeleton, in the evaluation of the disease and treatment response;
- role for biological agent assays and tests for antibodies to biological agents in the adjustment of the treatment regimen.

These practice guidelines will now be disseminated. In 2 years (2016), the task force plans to evaluate their impact and to decide, based on the availability of new data, on a revision date.

Disclosure of interest

D.W. conducts occasional interventions for AbbVie, BMS, MSD, Pfizer, Roche Chugai, Amgen, Nordic Pharma, UCB, SOBI, andet Sanofi Aventis and reports indirect interests in Abbvie, Pfizer, Roche Chugai, Servier, and MSD.

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B.C. reports long-lasting or permanent ties with MSD, Pfizer, Roche-Chugai, and UCB; as well as indirect interests (including grants or donations to an organization) in Pfizer and Roche-Chugai. He also conducts occasional interventions for Abbvie, BMS, Cellegen, Lilly, Nordic, Novartis, and Vertex.

F.G. conducts occasional interventions for GSK (scientific committee) and Pfizer (symposiums) and receives grants from Expansciences, Merck, and Sanofi.

C.H. conducts occasional interventions for Abbvie, Pfizer, Roche, UCB, MSD, and BMS. He also receives grants from Expansciences, Merck, and Sanofi.

C.M. conducts occasional interventions for Abbvie, BMS, Janssen, MSD, Pfizer, Roche-Chugai, and UCB and reports indirect interests in Abbvie, Pfizer, Roche-Chugai, and UCB.

M.D. receives honoraria paid to him personally for work as a consultant or speaker in the field of spondyloarthritis during satellite symposia organized by Pfizer, Abbvie, UCB, Eli-Lilly, Sanofi-Aventis, Roche, and Novartis. He is affiliated with the rheumatology department of the Cochin Teaching Hospital, AP-HP, Paris, France, which has received research grants for therapeutic trials in spondyloarthritis carried out with Pfizer, Abbvie, UCB, Eli-Lilly, Sanofi-Aventis,Roche, Novartis, Celgene, and Merck. Finally, he is the chief investigator of the DESIR cohort study, which is funded by a research grant from Pfizer.

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